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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/678,650	10/06/2003	Regine Hakenbeck	104049.B270037	7623

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EXAMINER	
WILDER, CYNTHIA B	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/678,650	HAKENBECK, REGINE	
	Examiner	Art Unit	
	CYNTHIA B. WILDER	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-12,14-17 and 20-23* is/are pending in the application.

4a) Of the above claim(s) *15-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,8-11,14,22 and 23* is/are rejected.

7)☒ Claim(s) *5,12 and 19-21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed April 3, 2009 is acknowledged and has been entered. Claims 7, 13 and 18 have been canceled. Claims 22-23 have been added. Claims 1-6, 8-12, 14-17, 19-23 are pending. Claims 15-17 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-6, 8-12, 14, 19-23 are discussed in this Office action. All of the arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. This action is made non-final as the new grounds of rejections presented in this Office action were not necessitated by Applicant's amendment of the claims. Accordingly, this Office action is deemed non-Final.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Previous Rejections

3. The prior art rejection under 35 USC 103(a) directed to claims 1 and 6 as being unpatentable over Dowson et al view of Kell et al is maintained and discussed below. The prior art rejection under 35 USC 103(a) directed to claims 2-3 as being unpatentable over Dowson et in view of Kell et al and further in view of *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995) is maintained and discussed below, but is withdrawn for the claims 11, 12, 14, 19 and 21 because the prior art does not teach the oligonucleotide of SEQ ID NOS: 18 and 19. The double patenting rejection is withdrawn in view of Applicant submission of a proper terminal disclaimer under 37 CFR 3.73(b).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dowson et al (citation made of record in prior Office action) in view of Kell et al (citation made of record in prior Office action). Regarding claim 1, Dowson et al. disclose a method for identifying penicillin-sensitive or penicillin-resistance streptococci previously not known to have antibiotic resistance comprising: isolating bacterial DNA and hybridizing the DNA with at least one sensitivity-specific DNA probe (Pn12) and at least one resistance-specific DNA probe (Pn11 and Pn13) (page 5859, right column second full paragraph) that specifically hybridizes to a DNA sequence specific to a penicillin binding protein gene (PBP2B) of penicillin sensitive strains of *Streptococcus pneumoniae* (page 5859, right column second full paragraph) and determining whether or not the streptococci strain is sensitive to penicillin or not by detecting which probe or probes hybridize (see page 5859 and Table 1, which recite Streptococci and strains wherein antibiotic resistance has not be determined (ND)) or wherein view little to high levels of resistance or sensitivity to penicillin has been determined).

Regarding Claim 6, Dowson et al. disclose the method wherein the probes are labeled radioactively (page 5859, right column, lines 4-6). Therefore, Dawson meets the limitations of the claims recited above.

Dowson et al do not expressly teach wherein the screening assay includes DNA from *S. pneumoniae* having unknown resistance to penicillin. However, Dowson provides sufficient evidence to the ordinary artisan to screen and/or test any streptococci strain having unknown resistance to penicillin using the claimed method steps. Dowson provides sufficient motivation for performing a screening assay as claimed using probes which specifically hybridizes to sequences specific to penicillin binding protein genes. Dowson et al teach in the introduction that the emergence of resistance to penicillin in a number of bacterial species has occurred by the development of altered high molecular weight penicillin-binding proteins that have reduced affinity for the antibiotic (page 5858). Dowson et al identifies regions in two of the PBP2B genes of penicillin resistant pneumococci that have been found to be altered in all penicillin resistance pneumococci and teaches wherein probes are designed to target this region in order to determine antibiotic resistance in Streptococci bacterial strains (page 5859).

Kell et al supports the teaching of Dowson et al. Kell et al teach that "penicillin resistance in Streptococcus pneumonia (the pneumonococcus) is entirely due to the development of altered forms of penicillin-binding proteins (PBPs) that have decreased affinity for beta-lactam antibodies". Kell et al teach that "the PBP genes of penicillin resistance pneumococci have a mosaic structure, consisting of regions that are very

similar to the corresponding regions in the genes from penicillin-susceptible pneumococci and regions that differ by as much as 20% in nucleotide sequences (see page 4382). Kell et al also teaches hybridization method steps using probe(s) targeted to sequences specific for PBP genes in order to fingerprint penicillin resistant pneumococci (see abstract 4383 and 4384).

Thus, it would have been obvious to one of ordinary skill in the art at the time of the claimed invention that the claimed invention of Dowson et al in view of Kell et al could be modified to screen any pneumococci sample having unknown penicillin resistance with a reasonable expectation of success. It would have obvious to a person of ordinary skill in the art to try to screen various DNA samples having no known penicillin resistance using the method of Dowson in view of Kell et al in an attempt to provide alternative means of screening for new or different strains of antibiotic resistant pneumococci for epidemiological studies as taught by both Dowson et al and Kell et al.

Response to Arguments

6. Applicant traverses the rejection on the following grounds: Applicant states that Dowson shows in Table 1 a number of penicillin sensitive and penicillin resistant streptococci, strains for which sensitivity or resistance to penicillin was known. Applicant states that clearly the designation ND, not determined means only that the MIC value was not measured, but this does not indicated that the bacteria sensitivity or resistance to penicillin was unknown. Applicant states that Downson as a whole does not teach or suggest determining whether the strains listed in Table 1 were sensitive or

resistant to penicillin using the method and oligonucleotides described in Dowson. Applicant states that Dowson does not teach or suggest or suggest that one of skill in the art can take any streptococci strain having unknown susceptibility to penicillin and then determine whether or not the strain is sensitive or resistant to penicillin by hybridizing its DNA with at least one sensitivity specific probe and at least one resistance specific probe and this does not provide any incentive for testing S. pneumonia in particular for resistance to penicillin. Applicant states that Kell does not teach or suggest fingerprinting any pneumococci wherein the sensitivity or resistance to penicillin was not known. Applicant states that the Kell does not overcome the deficiencies of Dowson.

7. All of the arguments have been thoroughly reviewed and considered but are not found persuasive. In response to Applicant arguments concerning the combined teachings of Downson et al in view of Kell, Applicant's attention is directed to *KSR Int'l Co. v. Teleflex Inc.* (550 U.S.____, 127 S. Ct. 1727 (2007)) where the Supreme Court determined that "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103 (*KSR*, 550 U.S. at ____, 82 USPQ2d at 1397)." The Supreme Court also determined that "[t]he combination of familiar elements according to known methods is likely to be

obvious when the combination does no more than yield predictable results (KSR, 550 U.S. at ___, 82 USPQ2d at 1395)."

In this case, the Examiner maintains once again that the claims as broadly written are not distinct from the teachings of the prior art because Dowson et al teach screening strains of S. pneumoniae along with other viridans streptococci to determine how specific probes (penicillin resistant specific probes and penicillin sensitive specific probes) hybridize to various Streptococcus strains (see pages 5859 and 5862). Additionally, like Applicant, Dowson focuses on the hybridization properties of the probes to determine the characteristics of the bacterial strains. The secondary teachings of Kell support the teachings of Dowson by focusing on methods steps of screening for penicillin resistant pneumococci, which the ultimate goal of the instant invention. The combination of Dowson in view of Kell clearly suggest that it is within the ordinary artisan technical grasp to screen a variety of sample for Streptococcus pneumoniae sensitivity or resistance using specific probes which target the PBP gene of penicillin resistance pneumococci.

In regards to Applicant's arguments concerning what is considered "known" and/or "unknown" with respect to penicillin resistance and sensitivity as currently claimed, it is noted that the term "known" and/or "unknown" as recited in the instant claims does not meaningfully distinguish anything structural in a claim because it represents a state of mind of the experimenter. To one experimenter, a particular property or sequence may be "known" while to another experimenter the same property or sequence is "unknown". The property or sequence is the same in either case. So

the term "known" does not have any structural weight and is akin to an "intended use" type recitation which receives little, if any, patentable weight. In this case, the identification of the property ("unknown resistance to penicillin) is based on the hybridization property to probe(s) that hybridizes to a PBP gene of penicillin resistant strains of Stretococcus pneumoniae. The combination of Dowson et al in view of Kell clearly provides a *prima facie* case of obviousness. Applicant's arguments are not found persuasive. Accordingly, the rejections are maintained.

Claim Rejections - 35 USC § 103

8. Claims 2-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dowson et al (citation made of record in prior Office action) in view of Kell et al (citation made of record in prior Office action) and further in view of *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995).

Regarding claims 2-3, Dowson et al. teach a method for identifying penicillin resistance in bacteria comprising: isolating bacterial DNA and hybridizing the DNA with at least one sensitivity-specific and at least one resistance-specific probe (page 5859, right column, and second full paragraph). Additionally, they teach that the PBP genes in penicillin sensitive and resistant strains of *S. pneumoniae* comprise highly conserved regions alternating with highly divergent regions (Abstract). Dowson et al. do not teach the sensitivity-specific probes are selected from SEQ ID NO: 7-13.

Kell et al. teach the PBP2x gene sequence of penicillin-resistant pneumococci and sequences which confer antibiotic resistance to pneumococci in patients wherein

said sequence comprises the sequence of SEQ ID NO: 8 (see accession number z21803 and Figure 4). Kell et al distinguishes between sequences of pneumococci that resistant and susceptible to penicillin (see page 4388).

In the court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties (see page 9, paragraph 4 of attached ref)."

Since the claimed sequence of the instant invention simply represent a structural homolog of the nucleotide sequences taught by Kell et al derived from sequences expressly suggested by the prior art of and known in the prior art as derived from PBP2x gene of penicillin-resistant pneumococci and useful for detecting penicillin resistance in Streptococci strains, and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed nucleotide sequences are *prima facie* obvious over the cited references in the absence of secondary considerations.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the PBP2x gene sequence differences

between antibiotic sensitive and antibiotic resistant strains and to use probes which hybridize to those sequences in the method of Dowson et al. for identifying antibiotic resistant bacteria for the obvious benefit of identifying clinically important antibiotic-resistant bacteria efficiently and economically using DNA hybridization and antibiotic response-specific probes.

Response to Arguments

9. Applicant traverses the rejections above on the following grounds: Applicant states that Dowson et al in view of Kell do not provide any incentive for one of skill in the art to make probes that can hybridize to various gene types of resistance, because such probes would not be specific for a particular class of resistance gene. Applicant states that the Kell teaches a sequence SEQ ID NO: 8 (noted by the Examiner) that is a sequence of the penicillin susceptible strain R6. Applicant states that SEQ ID NO: 8 does not confer any antibiotic resistance as it is not derived from the penicillin resistance pneumococci.

10. All of the arguments have been thoroughly reviewed and considered but not found persuasive for the reasons that follow: In response to Applicant's arguments concerning the combination of Dowson et al in view of Kell, the Examiner maintains the rejections on the same grounds previously discussed above at # 7. In response to Applicant's arguments concerning the sequence of Kell, it is noted that Kell teaches a sequence comprising a sequence 100% identical to SEQ ID NO: 8 as claimed in the instant invention (see claims and alignment below):

```
SEQ ID NO: 8          1 AACAGTTCTGCTGAAGAAG 19
                        ||||||||||||||||||
Kell                314 AACAGTTCTGCTGAAGAAG 332.
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Kell teaches that the sequence is part of the PBP 2X gene of penicillin resistant pneumococci (See Figures and attachment to reference mailed 3/20/2007). Kell further teaches isolating oligonucleotide sequences for use in PCR assays to fingerprint penicillin resistance strains of Streptococcus pneumoniae. Accordingly, the arguments are not found persuasive.

New Ground(s) of Rejections

The new grounds of rejections were not necessitated by Applicant's arguments. Accordingly, this action is made Non-Final.

.Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1, 4, 6, 8-11, 14, 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(a) Claims 1, 6, 8-10, are indefinite in the claims 1, 6, 8-10 for the limitation "specifically hybridizes" because the limitation has not be adequately defined in the instant specification and it cannot be determined what conditions are required for the instant invention to function properly. Additionally it cannot be determined from the claims as currently written what DNA probes are actually required to "specifically hybridize" and distinguish between penicillin resistance and sensitive S. pneumoniae as no actual structures of the probes have been defined in the instant claims.

Accordingly, given the ambiguity of the claim as currently written, it cannot be determined what conditions or specific probes are needed.

(b) Claims 4, 11, 14, 22 and 23 are indefinite for the recitation of "sequences which differ from one to four nucleotides" or "sequences which differ from one to four nucleotides under conditions that can permit hybridization" because the limitation is not adequately defined in the instant specification and it cannot be determined what one to four bases can be modified in order for the method to operate properly. The limitation as currently written suggests that any nucleotide change (mutation, SNP or variant) is within the scope of the instant. However, neither the claims nor specification supports this assertion; and thus it cannot be determine the metes and bounds of the limitation as it refers to the nucleotide modifications encompassed by the limitation.

Conclusion

13. Claims 1, 2, 3, 4, 6, 8-11, 14, 22 and 23 have been rejected. Claims 5, 12, 19-21 have been objected because they depend from rejected claims. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cynthia B. Wilder/
Examiner, Art Unit 1637